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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/776,933	02/10/2004	Bo Hansen	58614 (71432)	2102

21874 7590 05/31/2007
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EXAMINER	
SHIN, DANA H	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
05/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,933	HANSEN ET AL.	
	Examiner	Art Unit	
	Dana Shin	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2,4-9,14-16,47-50,53,54,91 and 93-105* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *98-105* is/are allowed.

6)☒ Claim(s) *2,4-9,14-16,47-50,53,54,91 and 93-97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

This Office action is in response to the communications filed on March 22, 2007.

Currently, claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-105 are pending. Applicant has cancelled claims 51-52.

The following rejections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 103

Claims 2, 4-9, 14-16, 48-50, 53-54, 91, and 93-97 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (WO 99/38963) in view of Thrue et al. (US 2004/0096848 A1) for the reasons stated in the Office action mailed on October 26, 2006 and for the reasons stated below.

Applicant's arguments filed on March 22, 2007 have been fully considered but they are not persuasive. Applicant argues that Wright et al. do not teach or suggest the compounds set forth in the instant invention and Thrue et al. do not make up for the deficiencies of Wright et al, and therefore, the combination of Wright et al. and Thrue et al. would not lead one of skill in the art to the claimed invention. Contrary to applicant's assertions, Wright et al. teach a number of different antisense compounds of 17 to 20 nucleotides in length, which are targeted to thioredoxin mRNA sequence as is the case with the instant application. See Table 1. Each of the 26 antisense oligonucleotide sequences set forth in Table 1 comprises at least 8 nucleotides of SEQ ID NO:8 consisting of "CAAGGAATATCACGTT". They teach that the thioredoxin antisense compounds include non-natural nucleotide analogs and/or phosphorothioate internucleotide linkages for increased nuclease resistance and/or increased uptake into cells (i.e., chemically modified nucleotides). See pages 8 and 14-17. They teach that the thioredoxin antisense oligonucleotides are administered in the form of pharmaceutical compositions, which further comprise pharmaceutically acceptable carriers or excipients of various formulations (pages 29-37). They teach that the pharmaceutical compositions comprising thioredoxin antisense oligonucleotides can further comprise an anticancer drug or a chemotherapeutic agent such as 5-fluorouracil and mitomycin-C (pages 9 and 39). They further teach that the thioredoxin antisense oligonucleotides can be inserted into expression vectors which confer sensitivity to the antiviral gancyclovir for enhanced therapeutic efficacy (page 40). Note that the disclosure of Wright et al. demonstrating pharmaceutical effects (i.e., reduction of tumor size in CD-1 nude mice) is fully enabled. See Figures 6A-6B. Although Wright et al. expressly teach incorporating non-natural nucleotide analogs into the thioredoxin antisense compounds, they do not teach that

the non-natural nucleotide analog is beta-D-oxy-LNA. However, this deficiency is cured by the teachings of Thrue et al.

Thrue et al. teach that beta-D-oxy-LNA is a superb form of nucleotide analogue because it exhibits unprecedented binding properties towards DNA and RNA target sequences (paragraph 0083). They teach that gapmers are chimeric oligonucleotides composed of beta-D-oxy-LNA and DNA, wherein DNA sequence is flanked by 1 to 6 residues of beta-D-oxy-LNA (paragraph 0096). They also teach that the LNA can be 5' methyl cytosine (paragraph 0056).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the thioredoxin oligonucleotides of Wright et al. in view of Thrue et al. One of ordinary skill in the art would have been motivated to combine the teachings of Wright et al. and Thrue et al. in order to make an effective thioredoxin antisense oligonucleotide compound comprising beta-D-oxy-LNAs in the form of a gapmer, because Thrue et al. teach that beta-D-oxy-LNA in the form of a gapmer is the most effective nucleotide analogue because of its binding affinity for the target sequence and the accessibility to the target site in target cells. The skilled artisan would have been motivated to combine the teachings of the prior art with a reasonable expectation of success because introducing modifications into nucleotides of antisense oligonucleotides was a routine task of optimization process as taught by Thrue et al. (paragraphs 0056, 0086, 0096) and Wright et al. (pages 8, 14-17). Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious in view of the combined teachings of the prior art.

New Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 103

Claim 47 is rejected under 35 U.S.C. 103(a) as being unpatentable over Wright et al. (WO 99/38963, of record) in view of Thrue et al. (US 2004/0096848 A1, of record) for the reasons stated in the Office action mailed on October 26, 2006 and for the reasons stated above.

Claim 47 was previously excluded from examination on the merits because it depended from a cancelled claim; however, it is now amended to depend from claim 91.

Claim 47 is directed to a conjugate comprising an antisense oligonucleotide having at least one LNA sugar and at least one non-nucleotide moiety covalently attached to said oligonucleotide.

Wright et al. teach a number of different antisense compounds of 17 to 20 nucleotides in length, which are targeted to thioredoxin mRNA sequence as is the case with the instant application. See Table 1. Each of the 26 antisense oligonucleotide sequences set forth in Table 1 comprises at least 8 nucleotides of SEQ ID NO:8 consisting of "CAAGGAATATCACGTT". They teach that the pharmaceutical compositions comprising thioredoxin antisense oligonucleotides can further comprise an anticancer drug or a chemotherapeutic agent such as 5-fluorouracil and mitomycin-C, which are non-nucleotide moieties (pages 9 and 39). Wright et al. do not teach LNA sugar modification.

Thrue et al. teach that beta-D-oxy-LNA is a superb form of nucleotide analogue because it exhibits unprecedented binding properties towards DNA and RNA target sequences (paragraph 0083).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the thioredoxin antisense oligonucleotide of Wright et al. with the LNA of

Thrue et al. and conjugate the LNA-modified oligonucleotide with an anticancer or chemotherapeutic agent as taught by Wright et al.

One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success because LNA modifications were known to increase specificity and binding affinity of antisense oligonucleotides as taught by Thrue et al., and because the composition comprising anti-thioredoxin antisense oligonucleotide conjugated with an anticancer or chemotherapeutic agent (non-nucleotide moiety) was known in the art as taught by Wright et al. Accordingly, the instantly claimed invention taken as a whole would have been *prima facie* obvious at the time of filing.

Conclusion

Claims 2, 4-9, 14-16, 47-50, 53-54, 91, and 93-97 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dana Shin whose telephone number is 571-272-8008. The examiner can normally be reached on Monday through Friday, from 8am-4:30pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Dana Shin
Examiner
Art Unit 1635

J. DOUGLAS SCHULTZ, PH.D.
SUPERVISORY PATENT EXAMINER